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September 24, 2004

Michael O. Leavitt, Administrator
US Environmental Protection Agency
P. O. Box 1473
Merrifield, VA 22116

Attention: Chemical Right to Know Program

Re: Response to EPA Comments on the Robust Summaries and HPV Test Plan for Allyl Alcohol (CAS # 107-18-6)

Lyondell Chemical Company (HPV Registration Number

Dear Mr. Leavitt:

Lyondell Chemical Company has reviewed EPA's comments and offers the following response. Most of the comments are taken, and, where the requested information is available, the robust summaries and test plan will be updated to incorporate the EPA comments with the exception of the recommendation to use OECD 421 rather than OECD414 for the Reproductive / Developmental end points.

In regard to the suggestion that Lyondell use the OECD TG 421 Reproductive / Developmental screening protocol study design rather than the OECD TG 414 Developmental Toxicity protocol, Lyondell has undertaken extensive review of our proposal and EPA's comments. After thorough consideration, Lyondell remains convinced that the 414 protocol is more appropriate protocol in this situation and is, in the long run, the most efficient and conservative option. Our rational is further explained in the following paragraphs.

Allyl alcohol causes significant toxicity following oral, dermal, or inhalation exposures. The robust summaries and test plan that have been prepared and provided to the EPA describes that the material as acutely toxic following ingestion, inhalation, or skin contact. The acute oral LD50 is in the range of 70 mg/kg in rats. The No-Observed-Adverse-Effect Levels (NOAEL) for subchronic administration is 6-8 mg/kg per body weight per day.

In addition, allyl alcohol is a well known liver toxicant and can cause extensive necrosis and covalent binding within the liver of rats. The mechanism of toxicity is well understood and is dependant upon the metabolism of allyl alcohol by alcohol dehydrogenase to form the chemicals acrolein and acrylic acid in the liver. These reactions can be inhibited by pyrazole and disulfuram (chemicals that inhibit alcohol and aldehyde dehydrogenation, respectively).

Chemicals that cause liver toxicity are also known to cause developmental toxicity by several different mechanisms. Many of these endpoints of developmental toxicity cannot be observed with the OECD reproductive developmental screening assay (OECD TG 421). In order to observe these types of

effects, a developmental toxicity study must be conducted which includes internal examination of the fetuses as is done with OECD TG 414.

In further support of this reasoning, it should be noted that Dr. Carl Keen of University of California at Davis has studied the significant effects of liver toxicity on developmental processes, and based on this work received the Josef Warkany Award at the 2004 Teratology Society Meeting in Vancouver, British Colombia, Canada. Dr. Keen has definitively demonstrated that materials that cause maternal liver toxicity and altered liver function can cause developmental toxicity through maternally-mediated mechanisms.

Since allyl alcohol is a well known liver toxicant, and the many of the effects observed in the fetus secondary to liver toxicity can only be found with a developmental toxicity study, Lyondell has proposed conducting a definitive developmental toxicity study.

Experiments conducted should always provide the best information possible for use in future risk assessments. If allyl alcohol did not have the toxicity profile described above, then a screening study would be appropriate. However, with the significant toxicity characteristics of this chemical, the wisest and most efficient course would be to conduct a definitive study and provide data useful for future risk assessment activities.

If Dr. Hernandez has any additional questions regarding the significance of liver toxicity on developmental end points, it should be noted that Health Effect Research Laboratory at the US EPA (Research Triangle Park, North Carolina), also has a research program trying to understand the effect of liver toxicity on developmental processes. Dr. John Rogers and Dr. Bob Kavlock of the US EPA have actively been engaged in this area of research for several years and understand the effect of liver toxicity on developmental processes. If a second opinion is needed to further address this concern, Dr. Rogers or Dr. Kavlock could be contacted.

It is reasonable to question whether these liver metabolites could reach the embryo to cause an effect on developmental processes. It is also important to question if these metabolites could be produced within the embryo/fetus itself and cause toxicity. Only a definitive developmental toxicity study provides the answers needed to fully address this question.

Lyondell Chemical thanks EPA for its review and comments and appreciates the opportunity to reply to Dr. Hernandez's letter.

If you have any questions, please contact me at 713.652.7339 or at claude.white@equistarchem.com.

Sincerely,

Dr. Wm. Claude White
Manager, Product Safety
Lyondell Chemical Company

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